NATURAL PRODUCT COLLABORATION AGREEMENT BETWEEN
SOURCE COUNTRY ORGANIZATION (SCO)
AND
THE DEVELOPMENTAL THERAPEUTICS PROGRAM
DIVISION OF CANCER TREATMENT AND DIAGNOSIS
NATIONAL CANCER INSTITUTE

The Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is currently screening synthetic compounds and natural product materials derived from plants, marine macro-organisms and micro-organisms as potential sources of novel anticancer drugs. The DTP is the drug discovery program of the NCI which is an Institute of the National Institutes of Health (NIH), an arm of the Department of Health and Human Services (DHHS) of the United States Government. While investigating the potential of natural products in drug discovery and development, NCI wishes to promote the conservation and sustainable utility of biological diversity, and recognizes the need to compensate source country organizations and peoples in the event of commercialization of a drug developed from an organism collected within their countries' borders.

DTP/NCI has an interest in investigating plants, terrestrial and marine micro-organisms and marine macro-organisms from [Source Country] and wishes to collaborate with the [Source Country Organization, SCO] in this investigation. DTP/NCI will make sincere efforts to transfer knowledge, expertise, and technology related to drug discovery and development to [SCO] in [Source Country, SC] (as the agent appointed by the [Source Country] Government), subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology. [SCO], in turn, desires to collaborate closely with the DTP/NCI in pursuit of the investigation of [Source Country]'s plants, terrestrial and marine micro-organisms and marine macro-organisms and selected synthetic compounds subject to the following conditions and stipulations of this Natural Product Collaboration Agreement (NPCA). [SCO] will perform the collection and processing of terrestrial plants, marine macro-organisms or micro-organisms as appropriate. It is understood that the [SCO] will be solely responsible for abiding by all source country's access policies and requirements for prior informed consent in the performance of collections. The NCI bears no responsibility for any contravention of such policies by the [SCO].

1) On the basis of in-house screening results in its anticancer screens, [SCO] may select both synthetic compounds and extracts of plants, marine macro-organisms and micro-organisms (subject to previously determined limits as to numbers per year) for anticancer testing at DTP/NCI. If suitable in-house screens are not available at [SCO], a list of available materials may be sent to DTP/NCI.

2) Prior to submission of the materials, [SCO] will send a data sheet, to be held in confidence by DTP/NCI, on each material so that DTP/NCI may check its databases for records of prior submission to DTP/NCI.

3) For pure compounds, the data sheet(s) will give pertinent available data as to chemical constitution, structure, available biological data including in-house screening results, solubility, toxicity and any precautions which need to be followed in handling, storage and shipping.

For crude extracts, data will be provided as to the source organism taxonomy, location and date of collection, any hazards associated with the organism, available biological data and any known medicinal uses of the organism/extracts.

4) DTP will inform [SCO] which of the materials are new to the program, and such materials will be shipped to DTP for screening. DTP will provide a record of the accession number for the materials. Quantities of materials required for initial testing are 5 mg for pure compounds and 10 mg for crude extracts.

5) a) Data provided by [SCO] will be considered as confidential information of [SCO], if so labeled, and will be held confidentially by DTP/NCI, unless the data are otherwise available from public sources. No confidential information of [SCO] will be kept in files open to the public either by DTP/NCI, testing laboratories, or data processing facilities, all of which are U.S. government contractors. Only those employees directly engaged in the operation of DTP/NCI will have access to the files of information regarding the source and nature of confidential materials, unless the release of data about the materials is required under law or by court order. In the event of expiration of this agreement, the confidentiality of data provided by the [SCO] will be maintained.

b) All test results will be provided to [SCO] as soon as they are available, but not later than 270 days (nine months) from the date of receipt of the sample. If available, *in vitro* test results will be delivered within 90 days from receipt of the sample. [SCO] will be informed in writing of any delays beyond this period (270 days) together with an explanation of the reason(s) for delay.

c) Unless the release of test results is required under law or by court order, the parties will keep the test results and subsequently-developed data confidential until published in accordance with Article 15 or until corresponding patent applications are filed in accordance with Article 9.

6) Any extracts exhibiting significant activity will be further studied by bioassay-guided fractionation in order to isolate the pure compound(s) responsible for the observed activity. Such fractionation will be carried out in [SCO] laboratories. If [SCO] has no available bioassay, DTP/NCI may assist [SCO] to establish the necessary bioassay systems subject to the availability of the necessary resources. Alternatively, or in addition, suitably qualified designated [SCO] scientists may be sent to DTP/NCI for the isolation studies subject to the terms stated below in Article 7. In addition, DTP/NCI may assist the [SCO], thereby assisting the

[Source Country], to develop the capacity to undertake drug discovery and development, including capabilities for the screening and isolation of active compounds from terrestrial and marine organisms.

7) Subject to the provision that suitable laboratory space and other necessary resources are available, DTP/NCI agrees to consider inviting senior technician(s) and/or scientist(s) designated by [SCO] to work in the laboratories of DTP/NCI or, if the parties agree, in laboratories using technology which would be useful in furthering work under this NPCA. The duration of such visits would not exceed one year except by prior agreement between [SCO] and DTP/NCI. The designated visiting scientist(s) will be subject to provisions usually governing Guest Researchers at NIH. Cost-sharing and other conditions of visits will be negotiated in good faith prior to the arrival of the visiting scientist(s).

8) In the event that an agent isolated and purified from materials provided by [SCO], and/or a synthetic compound provided by [SCO] meets the criteria established by the Drug Development Group (DDG) of NCI's DCTD (DTP's parent organization), which would include, but not be limited to, *in vivo* activity in rodent models, further development of the agent may be undertaken by DTP/NCI in agreement with the [SCO]. Further development of the specific agent may include but not be limited to analog development through medicinal and/or combinatorial chemistry, formulation, pharmacology and/or toxicology studies. Once an active agent is approved by DTP/NCI for preclinical development (*i.e.*, has passed the DDG at Stage IIA), DTP/NCI may collaborate with [SCO] scientists in the development of the specific agent.

9) Both [SCO] and DTP/NCI recognize that inventorship will be determined under patent law. DTP/NCI/NIH and [SCO] will, as appropriate, jointly seek patent protection on all inventions developed jointly under this Agreement by DTP/NCI and [SCO] employees, and will seek appropriate protection abroad, including in [Source Country], if appropriate. Application for patent protection on inventions made by [SCO] employees alone will be the responsibility of [SCO]. Application for patent protection on inventions made by DTP/NCI employees alone will be the responsibility of DTP/NCI.

With respect only to those compounds that have been determined to possess such significant anti-cancer potential as to be scheduled for clinical trials by DCTD, the U.S. Government shall have a royalty-free, irrevocable, nonexclusive license to manufacture and/or use by or for the U.S. Government the invention(s) claimed in any patents that [SCO] may have or may obtain on such compounds or on a process for use of such compounds. However, this license will apply only to [SCO] patents that rely upon data generated by DTP/NCI or DTP/NCI testing laboratories. This license shall be only for medical research purposes related to or connected with the therapy of cancer. The term "medical research purposes" as used herein shall not include treatment of patients outside of clinical trials or

commercial distribution of the compounds.

10) DTP/NCI will make a sincere effort to transfer any knowledge, expertise, and technology developed during such collaboration in the discovery and development process to [SCO], subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology.

11) All licenses granted on any patents arising from the collaboration conducted under the terms of this NPCA shall contain a clause referring to this NPCA and shall indicate that the licensee has been apprised of this NPCA.

12) Should an NCI/NIH patent on an agent discovered under this collaboration eventually be licensed to a pharmaceutical company for production and marketing, DTP/NCI will require that the licensee negotiate and enter into agreement(s) with [SCO] and/or an appropriate [Source Country] Government agency(ies) within twelve (12) months from the execution of said license. The agreement(s) will address the concern on the part of the [Source Country] Government that pertinent agencies, institutions and/or persons receive royalties and other forms of compensation, as appropriate.

Such terms will apply equally to inventions directed to a direct isolate from a natural product material, a product structurally based upon an isolate from the natural product material, a synthetic material for which the natural product material provided a key development lead, a derivative of a synthetic compound provided by [Source Country] or [SCO], or a method of synthesis or use of any aforementioned isolate, product, material or derivative; though the percentage of royalties negotiated as payment might vary depending upon the relationship of the marketed drug to the originally isolated product. It is understood that the eventual development of a drug to the stage of marketing is a long term process which may require 10-15 years.

13) In obtaining licensees, DTP/NCI will require that the applicant for license seek as its first source of supply the natural products available from [Source Country]. If no appropriate licensee is found who will use natural products available from [Source Country], or if [SCO] or their suppliers cannot provide adequate quantities of raw materials at a mutually agreeable fair price, the licensee will be required to pay to the [Source Country] Government or [SCO] as appropriate, compensation (to be negotiated) to be used for expenses associated with cultivation of medicinal organisms that are endangered or for other appropriate conservation measures. These terms will also apply in the event that the licensee begins to market a synthetic material for which a material from [Source Country] provided a key development lead.

14) Article 13 shall not apply to organisms which are freely available from different countries (i.e., common weeds, agricultural crops, ornamental plants, fouling

organisms) unless information indicating a particular use of the organism (e.g., medicinal, pesticidal) was provided by local residents to guide the collection of such an organism from [Source Country], or unless other justification acceptable to both [SCO] and DTP/NCI is provided. In the case where an organism is freely available from different countries, but a phenotype producing an active agent is found only in [Source Country], Article 13 shall apply.

15) Publication of data resulting from the collaboration under this NPCA will be undertaken at times determined by agreement between [SCO] and DTP/NCI. Before either party submits a paper or abstract for publication, the other party shall have sixty (60) days to review and as necessary, file a patent application in accordance with Article 9.

16) It is the intention of NCI that [SCO] not be liable to DTP/NCI for any claims or damages arising from NCI's use of the material provided by [SCO]; however, no indemnification for any loss, damage, or liability is intended or provided by any party under this NPCA. Each party shall be liable for any loss, claim, damage or liability, that said party incurs, as a result of said party's activities under this NPCA, except that the NCI, as an agency of the United States, assumes liability only to the extent as provided under the Federal Tort Claim Act (28 U.S.C. § 171).

17) DTP/NCI and its relevant contractors will not distribute materials provided by [SCO] to other organizations without written authorization from [SCO]. However, should [SCO] wish to consider collaboration with organizations selected by NCI for distribution of materials acquired through NCI collection contracts, DTP/NCI will establish contact between such organizations and [SCO].

18) [SCO] scientists and their collaborators may screen additional samples of the same materials for other biological activities and develop them for such purposes independently of this NPCA.

19) With the exception of Articles 1-4 and 6, all other Articles shall survive the expiration of this Agreement or its termination by the [Source Country] or [SCO]. Subsequent compounds and/or extracts may be submitted under the appropriate DTP/NCI mechanism and agreement.

This NPCA shall be valid as of the date of the final authorized signature below for an initial period of five (5) years, after which, it can be renewed by mutual agreement. It may be amended at any time subject to the written agreement of both parties. Copies of such amendments will be kept on file at both of the addresses indicated below. [SCO] and DTP/NCI are confident that this NPCA will lay the basis for a mutually successful cooperation in discovering and developing new therapies in the treatment of cancer.

For the [SCO]:

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_____
Date

mailing and contact address:

For the National Cancer Institute:

_____
Douglas R. Lowy, M.D.
Acting Director, National Cancer Institute

_____
Date

mailing and contact address:

Technology Transfer Center
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Riverside Five, suite 400
8490 Progress Drive
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